EVIDENCE-BASED CASE REVIEWS

Management of short stature

A 12-year-old girl is brought in by her mother, who is concerned because her daughter is short even compared with other family members. She estimates that her daughter has grown less than 3 cm (~1 in) in the past year and asks if she should receive growth hormone—a treatment that was recently mentioned in a newspaper article. The girl has no significant past medical illness or family history of disease that might be associated with short stature and is free of symptoms. She is a good student and has not been subjected to physical or verbal bullying at school. Her father is 170 cm (5 ft 10 in) tall (10th percentile for a man), and her mother is 160 cm (5 ft 3 in) tall (25th percentile for a woman). Neither was a "late bloomer." On physical examination, the prepubertal girl has no signs of disease. Her height is 133 cm (4 ft 4 in) (<5th percentile for age), and her weight is 35 kg (77 lb) (25th percentile).

Summary points

- Assessment for short stature requires accurate height measurements, taken serially and compared with population-appropriate height and height-velocity standards
- Short stature is most commonly familial or due to constitutional growth delay or a combination of both
- Short stature may rarely (in <5% of the shortest 1.3% of children) be associated with a serious underlying medical condition; treatable conditions need to be diagnosed early
- Short stature in childhood and adolescence is not usually associated with psychological disability, although bullying or babying and child or parental concerns about decreased adult socioeconomic success have been reported
- The use of human growth hormone to increase adult height in short but otherwise healthy children without growth hormone deficiency is controversial, and evidence regarding its effectiveness is extremely limited
- Future research should be directed at evaluating which diagnostic tests are valuable in assessing children with short stature, understanding the physical and psychosocial concerns of specific groups with short stature and the ethical implications of attempting to increase adult height, and testing proposed therapeutic interventions such as human growth hormone by controlled trials with well-defined clinical outcomes (eg, final adult height)

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BACKGROUND

Short stature is not a disease but a statistically defined height threshold. Some children with short stature are healthy, some have a medical condition known to be associated with short stature, and in some, short stature is the result of an undiagnosed illness. Parents and children who consult a physician about short stature may be concerned about either the possibility of an underlying disease or perceived social discrimination because of short stature, including teasing or bullying in school or decreased future socioeconomic success.[1] In the past 15 years, the manipulation of human stature has become an area of intense biologic and psychological research, controversial clinical practice, substantial commercial interest, and important ethical debate.[2,3]

Growth assessment requires accurate measurements of height and weight over time, the measurement of parental height, pubertal staging, and the selection of appropriate group reference standards.[4-6] The definition of short stature has varied with time and place. On some growth charts, short stature is defined as a height of less than the fifth percentile for age. On others, it is defined as the lower limit of normal for height at the 3rd and even the 0.4th percentile for age.[7,8] To measure height, it is essential to use a stable wall-mounted device that has been accurately installed and is regularly calibrated and to ensure that trained personnel correctly position the patient. Repeating the measurement reduces error. The height should be recorded and plotted on a growth chart. Height velocity is obtained by taking two accurate height measurements at least 6 months apart and comparing with standard height-velocity data. Parental heights may be used to estimate a target height percentile. The final height range can be estimated by taking the average of the heights of the biologic parents, adding 6.5 cm (2.5 in) if the patient is male or subtracting 6.5 cm if the patient is female, and drawing a target range around this point on the growth chart to represent plus or minus 10 cm (4 in). When needed, radiographic bone age should be determined by a specialist in the technique.

FORMULATING CLINICAL QUESTIONS

Several questions need to be answered before the appropriate diagnostic workup and the need for interventions to increase height are chosen. You frame your questions to help structure a search of the literature.

- In children (population) presenting with short stature (exposure), what is the frequency of an underlying medical disorder (outcome)? [baseline risk]
- Is short stature (exposure) during childhood (population) associated with psychological disability (outcome)? [harm]
- In children (population) with short stature but without underlying disease (exposure), does growth hormone supplementation (intervention) increase adult height (outcome)? [therapy]

General approach to searching for evidence

You first look for summarized evidence, such as high-quality systematic reviews and evidence-based guidelines, to answer your questions. Issue 5 of the British publication, *Clinical Evidence,* has nothing on short stature. The Cochrane Library's *Database of Systematic Reviews* contains a recent review of the use of growth hormone in children with chronic renal failure but no reviews of its use in other conditions.[9] The Cochrane *Clinical Trials Register* lists numerous studies of the use of growth hormone in various conditions associated with short stature, including Turner syndrome, idiopathic short stature, growth hormone deficiency, Prader-Willi syndrome, and intrauterine growth retardation. You also search MEDLINE through WinSPIRS and PubMed's Clinical Queries feature (box 1).

CRITICAL REVIEW OF THE EVIDENCE

Frequency of underlying medical disorder in short stature

Between 1985 and 1987, the Wessex Growth Study investigators attempted to measure all children at 5 years of age (school entry) in two adjacent health districts in Wessex, England.[10] Those detected by the nurses to have short stature (height <3rd percentile according to the Tanner-Whitehouse standards) had thyroid function and blood chemistry tests and bone age estimates, with referral to a specialist pediatrician if the results were abnormal. This cross-sectional study fulfills the validity criteria for a study of disease probability, as reviewed by Richardson and colleagues.[11] The study patients are representative of the full spectrum of those who would be seen in primary care, the diagnostic workup was fairly comprehensive and consistently applied, and undiagnosed patients were observed for an additional year. Thus, the data from this study should be applicable to groups in developed countries even 15 years later.

In total, 14,346 children were screened, and 180 (1.3%) were found to have short stature. Of these 180 children, 25 were known to have a known diagnosis consistent with short stature, such as trisomy 21, hypochondroplasia, Turner syndrome, Russell-Silver syndrome, celiac disease, or conditions with severe skeletal malformation. Five children belonged to ethnic groups for which the growth standards were deemed inappropriate, and three families declined to participate in the study. Eight children were diagnosed with an underlying disease as a result of the screening program, including Noonan syndrome, hypothyroidism, celiac disease, lead poisoning, neurofibromatosis, and growth hormone deficiency. The

Box 1 Search strategy: MEDLINE

Question 1

MEDLINE, using WinSPIRS 4.0: Body-height, all subheadings AND mass screening, all subheadings

Question 2

- PubMed Clinical Query, search term: *short stature*; category: prognosis; emphasis: specificity
- PubMed Clinical Query, search term: *short stature AND psychol*;* category: etiology; emphasis: specificity

Question 3

- PubMed Clinical Query, search term: *short stature AND growth hormone;* category: therapy; emphasis: specificity
- MEDLINE search term: *exp* [expand] *growth hormone/all subheadings AND randomized controlled trials* (textword)

remaining 139 healthy children with short stature were observed for 1 year to confirm that they had normal height velocity. In this large study, about 18% of children identified to have short stature at school entry were found to have an underlying medical condition that was previously undiagnosed in about 5% (95% confidence interval [CI], 0%-14%).

Growth hormone deficiency was not well studied in the Wessex study, so you look at the study of the prevalence of growth hormone deficiency by Xiu-lan and associates.[12] This study also fulfills the validity criteria of Richardson et al.[11] School physicians measured all 103,753 students aged 6 to 15 years in two districts of Beijing. The 202 children confirmed to have short stature (<3rd percentile for age by northern Chinese standards but less than the 0.2 percentile for the Beijing population) were comprehensively evaluated. Of these children, only 13 (6% of those with short stature) were diagnosed as having medical conditions other than growth hormone deficiency. Using a strict definition of growth hormone deficiency, seven children with height below the 0.2 percentile were found to have "total" growth hormone deficiency—a prevalence of 1 per 15,000, or 3.5% (95% CI, 1.0%-6.4%).[13]

Finally, you create a list of conditions, including rare diseases, that may cause short stature and are important to diagnose because of their severe prognosis or potential for treatment (see box 2), using your textbook as a second source. Common variants of normal that may present with short stature are clinically defined by normal height velocities in mid-childhood and either delayed bone age (for constitutional delay) or short parents (for familial short stature), or a combination of both. Sensitive and specific tests are available to diagnose some of the rarer causes of short stature: for example, thyrotropin level for primary hypothyroidism and karyotype for Turner syndrome. For other conditions (such as gastrointestinal diseases), the specific tests are invasive. You find no concise summary of evidence on the diagnostic properties of tests for disorders that cause short stature.

Box 2 Causes of short stature

Common causes*
- Familial short stature
- Constitutional delay of growth and puberty
- A combination of the 2

Rarer causes

Genetic syndromes
- Turner syndrome
- Hypochondroplasia
- Russell-Silver syndrome
- Intrauterine growth retardation with failure to "catch up"

Gastrointestinal disease
- Celiac disease
- Inflammatory bowel disease

Endocrine disease
- Acquired primary hypothyroidism
- Growth hormone deficiency
- Steroid-induced growth failure
- Pseudohypoparathyroidism

Renal disease
- Renal failure
- Renal tubular acidosis

*No underlying disease is found in >95% of short children.

Short stature in childhood and psychological disability

The first search through PubMed (*prognosis of short stature*) yields one review article that concludes that "short stature is not associated with clinically significant psychologic morbidity."[14] The second search (on short stature as a cause of psychological problems) yields only one primary article.[15] The authors tested the hypothesis that referral bias had influenced an earlier study finding that children with short stature were academically and socially handicapped. Random samples of children with and without short stature were recruited in parallel from the public school system and from pediatric endocrinology specialty clinics. The average age of each group was between 9 and 10 years. A battery of psychosocial tests was used, including tests for intelligence and educational achievement (completed by the children), family cohesion and adaptability (completed by the parents), and adaptive problematic behavior (completed by the teacher). Comparison groups were clearly defined and measured for height and psychosocial state independently and consistently and at a relevant age. The community-based participants were randomly selected from the group, and there were no obvious confounders. However, the group numbers were small (about 30 per group), and issues of sample size, power, and properties of the measurement scales were not addressed in the article. The authors found that the short children who were referred to specialists had more externalizing behavioral problems and poorer social skills than those with normal stature. No differences were found between community participants with and without short stature, so the criteria for assessing harm (causation) could not be applied.[16]

Role of growth hormone in short children with no underlying disease

The search through PubMed finds only one article that describes a recent randomized trial on the use of growth hormone, but with no results on final height available.[17] The other search of MEDLINE yields one systematic review, performed 10 years after the introduction of biosynthetic human growth hormone, which identifies randomized controlled trials (RCTs) and their limitations.[18] Only five RCTs on the use of interventions in healthy children were listed: four studies of human growth hormone and

one study of gonadotropin-releasing hormone. Of these five, only one has published adult height results.[19] Two trials have examined the use of human growth hormone in patients with Turner syndrome, one of which published results in abstract form only. No published trials to adult height in patients with any other diagnosis are available.

The article by McCaughey and colleagues is the only RCT of the use of growth hormone to increase adult height in healthy short children.[19] This study recruited 18 girls (mean age, 8.0 years) of 40 eligible from the Wessex Growth Study. Of these 18, data were available on the 13 who completed the trial (7 treated subjects and 6 control subjects). The mean duration of treatment was 6.2 years. The trial initially used randomization to create two groups; however, the loss of 5 (28%) of the 18 subjects could have influenced results. The adult height difference between groups was 7.5 cm (3 in). All seven treated subjects had heights within their target range, but only 3 of 6 control subjects had heights within the target range. Hence, two patients would need to be treated (number needed to treat = 2) to result in one additional child reaching the target height (95% CI, 1-10). There are three statistical concerns with adopting this evidence: this is the only published RCT of its kind; the sample size is small, leading to large CIs; and the original study recruited both boys and girls, who may have different responses to therapy. The study needs to be replicated to confirm its results.

From the history taking and findings of the physical examination, you are able to reassure the child and her mother that nothing suggests that the child has an underlying disease that might be associated with short stature. She has no evidence of psychological difficulties associated with her short stature, and you reassure them that such difficulties are uncommon in otherwise healthy children. The child is shorter than expected, based on the parents' heights, and because the mother reports poor linear growth, you obtain bone age radiographs. You do some screening tests to exclude rare causes of short stature that would be important to treat—hypothyroidism, Turner syndrome, inflammatory bowel disease, renal failure or renal tubular acidosis, and hypoparathyroidism. The bone age is delayed, but the blood test values are normal. You explain that constitutional growth delay is the most likely cause of the girl's short stature and make an appointment for 6 months later to measure height, calculate height velocity, and assess pubertal status. If the patient has an abnormal height velocity, specialist referral will be necessary to assess for acquired growth hormone deficiency and, if growth hormone deficiency is present, to arrange imaging to exclude a central nervous system tumor. You explain to the family that there is insufficient evidence to justify the use of growth hormone in healthy children who do not have growth hormone deficiency or another underlying medical condition.

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